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Keywords

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Disciplines

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Protecting Group Effects on the Efficiency of the Ruthenium Catalysed Alder-ene Reaction

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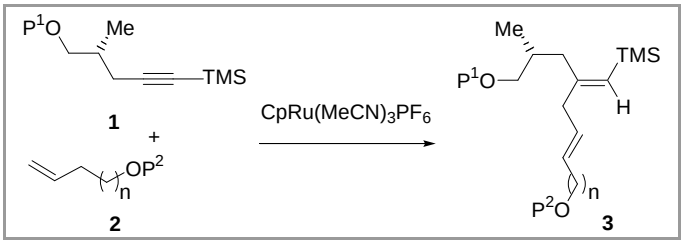
Abstract: The efficiency of the ruthenium-catalysed Alder-ene reaction of hydroxy alkenes depends heavily on the nature of the *O*-protecting groups employed as well as the length of the carbon spacer between the hydroxy and alkene group.

Key words: Alder-ene reaction, ruthenium catalysis

The ruthenium catalyzed Alder-ene reaction is an atom efficient process that can provide trisubstituted alkenes in a highly stereodefined manner.[1] As part of a current project we required the synthesis of the differentially protected trisubstituted alkene **3** (n=1), via the ruthenium catalyzed Alder-ene reaction between the alkyne and alkene components **1** and **2**, respectively (Scheme 1). In pursuit of this goal we found that the nature of the protecting groups P^1 and P^2 had a dramatic effect on the efficiency of this coupling process. We report here the results of this investigation and those of a study on related coupling partner, $PMBO(CH_2)_4C{\equiv}CTMS$ (**4**).



Scheme 1

The results of the study of the ruthenium catalyzed Alder-ene reactions of **1** and **4** with alkenes **2** are shown in Table 1.

Trimethylsilylalkynes **1** or **4** were stirred with excess alkene **2** (5 equiv) in the presence of catalytic (20-30 mol%) $CpRu(MeCN)_3PF_6$ in dry acetone at room temperature.[2] In each case only one regio- and geometric isomer of the 1,4-diene product **3** was obtained. The new C-C bond is formed distal to the trimethylsilyl group and the new double bond formed is of (*E*) geometry.

The efficiency of the Alder-ene reaction appears to depend heavily on the nature of the protecting group P^2 and the length of the carbon-carbon chain of **2**.

Initial studies focused on the coupling of silylalkynes **1** and **4** bearing a PMB protecting group. Whilst homoallylic alcohol gave no reaction and just returned starting materials, the TBDPS ether gave the desired 1,4-dienes in moderate yields (entries 1-4).

Table 1 Alder-ene Reaction of Trimethylsilylalkynes[a]

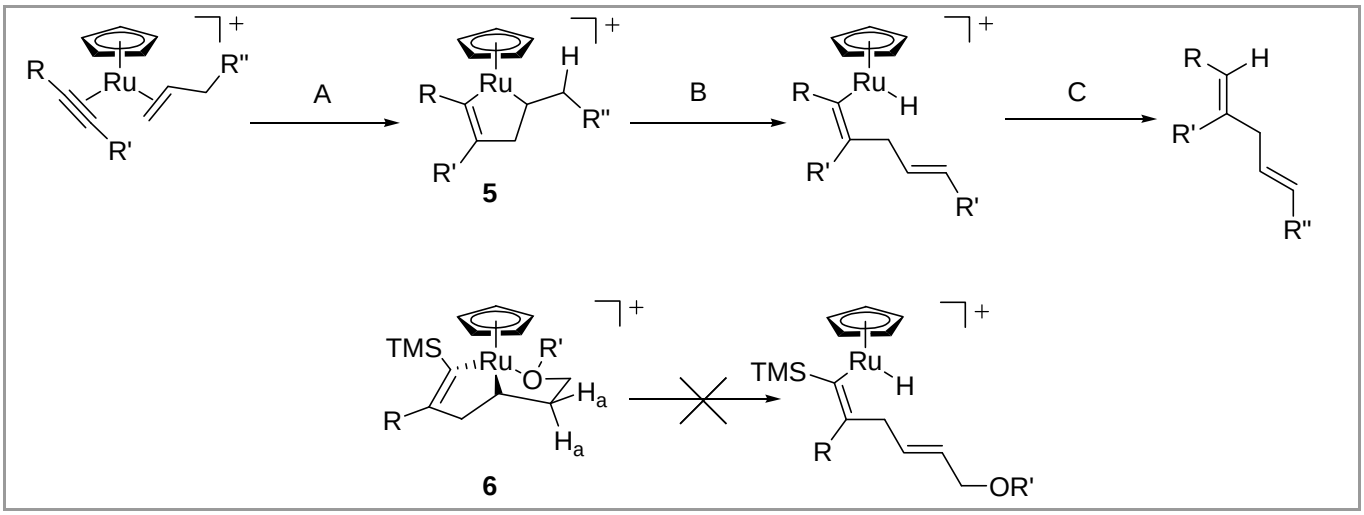
Entry	Alkyne/P^1	P^2	n	Yield (%)[d]
1	**4**/PMB	H	1	0[b]
2	**4**/PMB	TBDPS	1	67[b]
3	**1**/PMB	H	1	0[b]
4	**1**/PMB	TBDPS	1	50
5	**1**/TBDPS	H	1	0
6	**1**/TBDPS	PMB	1	14
7	**1**/TBDPS	Ac	1	85
8	**1**/TBDPS	Me	1	0
9	**1**/TBDPS	PNB	1	98[b,c]
10	**1**/TBDPS	H	2	96
11	**1**/TBDPS	Ac	2	79[b,c]
12	**1**/TBDPS	PMB	2	19[b,c]
13	**1**/TBDPS	Bn	2	48[b]
14	**1**/TBDPS	PNB	2	93[b,c]
15	**1**/TBDPS	H	3	99[c]
16	**1**/TBDPS	Ac	3	99
17	**1**/TBDPS	PMB	3	18

[a]Reaction conditions: 30 mol% $CpRu(MeCN)_3PF_6$, alkene:alkyne 5:1, acetone, rt, 20 h.
[b]20 mol% catalyst.
[c]Reaction time 4h.
[d]After purification by column chromatography.

When the protecting groups P^1 and P^2 were reversed the reaction was very sluggish (entry 6). Further investigation into the compatibility of the protecting groups P^1 and P^2 was undertaken in order to develop an efficient synthesis of **3**. These studies uncovered a number of interesting trends.

The ene-yne coupling proceeds most efficiently when protecting group P^2 is of an electron-withdrawing nature, for example an acetate or *p*-nitrobenzyl (PNB) (entries 7, 9, 11, 14 and 16). The 1,4 diene is formed in excellent yield regardless of the carbon-carbon chain length of the alkene **2**.

The use of 3-buten-1-ol or its *O*-methyl ether derivative had a detrimental effect on the course of the reaction, and only starting materials were recovered (entries 1, 3, 5 and 8). Intriguingly, the homologues, 4-penten-1-ol and 5-hexen-1-ol proved excellent substrates affording the 1,4-hepatadien-7-ol and 1,4-octadien-8-ol products in excellent yields (entries 10 and 15). A strong electronic effect was observed with alkenes bearing substituted



Scheme 2

benzyl ethers. The electron rich PMB ethers were poor substrates, affording less than 20% yield of **3**, regardless of the carbon-carbon chain length (entries 6, 12 and 17). In these reactions the low yields were due to incomplete reaction of **1** and **2.** 1-Benzyloxy-3-butene affords a moderate yield (entry 13), whilst the electron deficient PNB ethers of 3-buten-1-ol and 4-penten-1-ol couple efficiently (entries 9 and 14).

The established mechanism[1b,c] for the Ru-catalysed Alder-ene reaction involves oxidative addition of the coordinated alkene and alkyne to form ruthenocyclopentenes of the type **5** (step A, Scheme 2), which undergo *β*-hydrogen elimination and reductive elimination to give the 1,4-diene products (steps B and C). In the case of the Alder-ene reaction of 3-buten-1-ol and its *O*-methyl derivative, there is the possibility of coordination of the oxygen to the ruthenium, generating a pseudocycle (see **6**). This remote binding would force the dihedral angles between C-Ru and C-H_a to be >90°, and geometrically preclude *syn*-*β*-hydrogen elimination of protons H_a.[3,4] Intermediate **6** is consistent with our observations, given that extension of the carbon spacer may reduce internal coordination or allow efficient *β*-hydrogen elimination to occur because of the larger ring size (entries 10 and 15).

The well-documented affinity of the cationic $CpRu^+$ moiety for arene rings[6] may explain the substituent effects observed in the Alder-ene reaction of benzyl protected alkenols. We postulated that in the course of the reaction PMB-bearing substrates and/or products may be forming sandwich complexes of the type $[CpRu(\eta^6\text{-arene})]^+$ and thus inhibiting the reaction.[7] To investigate this possibility a d^6-acetone solution of $CpRu(MeCN)_3PF_6$ was treated with an excess of 1-(4-methoxybenzyloxy)-3-butene and mixed at room temperature for 30 minutes. The ^{1}H NMR spectrum of the solution showed a new multiplet at 6.32-6.53 ppm, consistent with Ru-complexed aromatic H peaks,[8] while the Cp peak had shifted upfield slightly to 5.48 ppm, thus supporting the formation of $[CpRu(\eta^6\text{-arene})]PF_6$ complex **7**. A reduction in the concentration of the PMB group in the reaction mixture should reduce the quenching of the catalyst. Indeed, the Alder-ene reaction of alkyne **1** (P^1=TBDPS) with alkene **2** (n=1 and P^2=PMB) is more efficient when a 1:1 molar ratio of reagents is used, rather than a large excess of alkene, resulting in a 38% conversion to the 1,4 diene (c.f. entry 6).

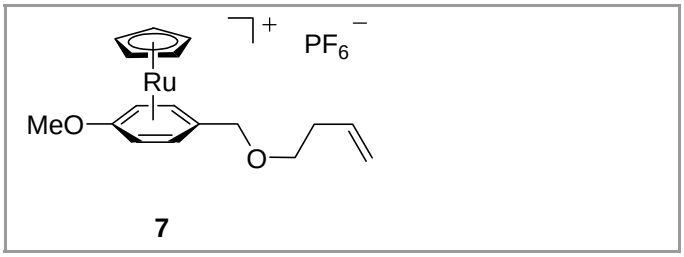


Figure 1

In conclusion, we have demonstrated that the efficiency of the ruthenium-catalysed Alder-ene reaction of 3-buten-1-ol derivatives with silylalkynes depends heavily on the protecting groups employed. By careful choice of electron deficient *O*-protecting groups on the alkene substrate efficient Alder-ene coupling can be achieved. Furthermore, *p*-methoxybenzyl *O*-protected hydroxy alkenes were found to be poor substrates in the three examples tried.

Acknowledgment

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(2) (1*Z*,4*E*)-(*R*)-1-trimethylsilyl-2-(2'-methyl-3'-*tert*butyldiphenylsilyloxy)-6-acetoxy-1,4-hexadiene. $CpRu(MeCN)_3PF_6$ (39 mg, 0.09 mmol) under Ar was treated with an acetone solution (2 mL) of 1-acetoxy-3-butene (170 mg, 1.5 mmol) and (*R*)-1-(trimethylsilyl)-4-methyl-5-(*tert*butyldiphenylsilyloxy)-1-pentyne (123mg, 0.3 mmol). The yellow solution was stirred at RT for 20 h. The reaction mixture was passed through a short plug of silica and concentrated *in vaccuo*. The residue was purified by column chromatography (increasing polarity from 1 % to 10% EtOAc in pet. sp.), which gave the title compound (134 mg, 0.256 mmol, 85 % yield) as a colourless oil. R_f (11 % EtOAc in pet. sp.): 0.67. $[\alpha]_D^{25}$: + 1.1 (c 6.7, CH_2Cl_2). MS (ES+): *m*/*z* (%) = 463.28 (100) [M-OAc], 540.32 (23) [$M+NH_4^+$], 545.29 (33) [$M+Na^+$], 561.26 (12) [$M+K^+$], 655.20 (33) [$M+Cs^+$]. HRMS (ES+): *m*/*z* [$M+Na^+$] calcd for $C_{31}H_{46}O_3NaSi_2$ 545.2883; found: 545.2904. δ_H (300 MHz, $CDCl_3$): 0.06 (9H, s, $(C\underline{H}_3)_3Si$), 0.86 (3H, d, *J*=6.0 Hz, $C\underline{H}_3CH$), 1.06 (9H, s, $(C\underline{H}_3)_3CSi$), 1.82-2.02 (2H, m, $CH_3C\underline{H}$ and $CHC\underline{H}_2C$=), 2.05 (3H, s, $C\underline{H}_3C(O)O$), 2.27 (1 H, dd, *J*=12.9, 4.8 Hz, $CH_3C\underline{H}$), 2.74 (2H, d, *J*=6.6, =$CHC\underline{H}_2CH$=), 3.47 (2H, d, *J*=6.0 Hz, $C\underline{H}_2OSi$), 4.52 (2H, d, *J*=6.3 Hz, $C\underline{H}_2OAc$), 5.23 (1H, s, TMSC$\underline{H}$), 5.54 (1H, dt, *J*= 15.3, 6.3 Hz, $AcOCH_2C\underline{H}$=CH), 5.73 (1H, dt, *J*= 15.6, 6.9 Hz, $AcOCH_2CH$=C$\underline{H}$), 7.36-7.44 (6H, m, SiPh), 7.62-7.68 (4H, m, SiPh). δ_C (75 MHz, $CDCl_3$): 0.8 (CH_3), 16.4 (CH_3), 19.5 (C), 21.2 (CH), 27.2 (CH_3), 34.2 (CH_3), 39.6 (CH_2), 41.8 (CH_2), 65.3 (CH_2), 69.5 (CH_2), 125.8 (CH), 126.8 (CH), 127.8 (CH), 129.8 (CH), 134.1 (C), 134.3 (CH), 135.9 (CH), 155.3 (C), 171.0 (C=O).

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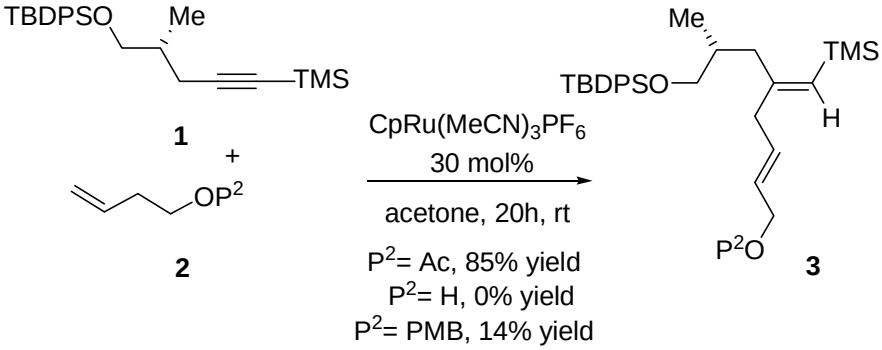

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